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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/785,895	02/16/01	BELARDINELLI L	MBHB00-081-A

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EXAMINER	
SCHMIDT,M	

ART UNIT	PAPER NUMBER
1635	4

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/785,895	BELARDINELLI ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-18 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-18 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite for failing to include a final step which relates back to the preamble. Specifically, the preamble claims a "method for inhibiting the proliferation of mammalian cells that express the A2B adenosine receptor" but the method steps do not indicate a final step wherein the proliferation of mammalian cells has been inhibited.

Claim 1 lacks antecedent basis for "the mammal".

Claim 3 lacks a conjuction in lines 2 and 3 so that the relationship between endothelial cells and those from the vascular bed is clear.

Claim 5 lacks antecedent basis for "the endothelial cells".

Claim 11 appears to have a typographical error in line 2: "raging" should be written "ranging".

Claim 12 lacks antecedent basis for "the adenosine A2B adenosine receptor".

Claim 14 lacks antecedent basis for "agonist" since claim 1 is drawn to antagonists of the A2B receptor.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for design and administration of A2B antagonists to cells in culture, does not reasonably provide enablement for design and administration of A2B antagonists to cells in whole organisms for the claimed therapeutic benefits. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-15 are drawn to methods for inhibiting the proliferation of mammalian cells that express the A2B adenosine receptor comprising administering a therapeutically effective amount of an A2B adenosine receptor antagonist to the mammal. The dependent claims specify wherein the cells that express the A2B adenosine receptor are vascular endothelial cells, such as coronary endothelial cells, endothelial cells from the vascular bed, tumor endothelial cells, retinal

endothelial cells, retinal endothelial cells, dermal endothelial cells, brain endothelial cells; wherein the A2B adenosine receptor antagonist inhibits the expression of vascular endothelial cell growth factor (VEGF); wherein the A2B adenosine receptor antagonist is an A2B adenosine receptor antisense oligonucleotide or A2B-specific ribozyme; wherein the antagonist is a non-selective adenosine receptor antagonist; wherein the antagonist is a selective A2B adenosine receptor antagonist; wherein the antagonist is administered in an amount ranging from about 1 microgram/kg to about 50 miligrams/kg or to about 10 miligrams/kg; wherein the adenosine receptor antagonist is administered by a method selected from the group consisting of orally, nasally, transdermally by bolus, intravenously, in eye drops, by inhalation, and by using micropumps; wherein the antagonist is administered in eye drops; wherein the mammal is a human.

The specification as filed teaches by way of example administration of the A2B antagonists JW-V1-08 and 3-N-propylxanthine (selective) and NECA (non-selective) in human retinal endothelial cells (HREC cells). The specification teaches prophetic design of other A2B antagonists and use in other cell types, including administration to a whole organism for therapeutic purposes. The art (see the art rejections below) further teaches administration of A2B antagonists to cells in culture, but does not support an expectation of success for design of any A2B antagonist for administration to cells in whole organisms as broadly claimed.

While the specification is enabling for design of A2B antagonists for administration to cells in culture, neither the specification nor the art provide sufficient guidance for the design and/or

administration of any A2B antagonist for cells in a whole organism, as presently claimed. The art teaches that the A2B receptor has been identified in many different cell types in the whole organism. The claims broadly read on administering "a therapeutically effective amount of an A2B adenosine receptor antagonist to the mammal" and thus reads on administration to any mammal.

There is a high level of unpredictability in the art for design of functional therapeutic compounds for use in any whole organism as broadly claimed. Mammals are known to differ in their physiology so that success of a drug in one whole organism does not necessarily correlate to success of the same drug in another whole organism. Factors such as toxicity of the compound, stability in vivo, routes of administration and target specificity/availability, etc. are factors which vary greatly. There is no general guidance known in the art for design and administration of any drug therapeutic compound to whole organisms. As such, although the specification and the art teach design of A2B receptor antagonists, there is no guidance in either the specification or the art to suggest that these compounds would function in a whole organism for the broadly claimed therapeutic functions of inhibiting proliferation of mammalian cells that express the A2B adenosine receptor.

To exemplify the problems associated with one type of claimed drug, antisense to A2B receptor: the factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find

and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included.

Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*.

Similar considerations exist for ribozymes, and other drugs, such as small molecules and protein drugs, which could be considered antagonists of the A2B receptor. There simply is no known formula for designing an antagonist with known in vivo fucntion for specific therapeutic functions. Further, in view of the fact in the instant case that A2B adenosine receptors are known to be located in several types of endothelial cells, it is unclear how one of skill in the art would target a specific type of tissue for therapeutic purposes and/or whether the antagonism of all accessible A2B receptors in cells in whole organisms would be an undesired side-effect. It is unclear based on such information that the receptor is located in many bodily tissues in the human, what specific diseases one skill in the art would use any such A2B antagonist to treat. Thus one skilled in the art would necessarily practice basic research to identify which diseases are treatable by such drugs. Further, as many of the 35 U.S.C 103 references below teach, although there are known adenosine receptors in the art, the A2B receptor is the least characterized and specific agonists and antagonists were not known at the time the invention was made. Thus the

administration of general, non-specific agonists would have additional side effects not only associated with any A2B mediated diseases. Neither the specification nor the art address the design of pharmaceutics which would enable one skilled in the art to successfully design such A2B drugs ready for in vivo use without a significant amount of "trial and error" experimentation common to the entire field of drug development for targeting a specific agent in the whole organism.

The lack of guidance in the specification as filed for these factors would therefore require undue experimentation beyond which is taught by the specification as filed to practice the invention as claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 16-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Grant et al.

Claim 16 is drawn to a method for assaying compounds to determine if they are A2B adenosine receptor antagonists or A2B adenosine receptor agonists comprising the steps of : (a) preparing a first and second sample of human retinal endothelial cells, (b) adding a compound to be tested to the first sample of human retinal endothelial cells and allowing the compound to

remain in contact with the first sample of human retinal endothelial cells for a defined period of time; and (c) comparing the number of new cells grown in the first sample with the number of new cells grown in the second sample. Claim 17 is drawn to an A2B adenosine receptor antagonist compound identified by the method of claim 16 wherein the compound caused fewer new cells to grow in the first sample in comparison to the second sample. Claim 18 is drawn to an A2B adenosine receptor agonist compound identified by the method of claim 16 wherein the compound caused more new cells to grow in the first sample in comparison to the second sample.

Grant is relied upon to teach design of an antisense to A2B receptor and administration to human retinal endothelial cells and comparison of the cell growth. (see pages 703-705)

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grant et al. and Kvanta et al. in view of Kemp et al., Kim et al. and Klotz et al.

Claim 16 is drawn to a method for assaying compounds to determine if they are A2B adenosine receptor antagonists or A2B adenosine receptor agonists comprising the steps of : (a) preparing a first and second sample of human retinal endothelial cells, (b) adding a compound to

be tested to the first sample of human retinal endothelial cells and allowing the compound to remain in contact with the first sample of human retinal endothelial cells for a defined period of time; and (c) comparing the number of new cells grown in the first sample with the number of new cells grown in the second sample. Claim 17 is drawn to an A2B adenosine receptor antagonist compound identified by the method of claim 16 wherein the compound caused fewer new cells to grow in the first sample in comparison to the second sample. Claim 18 is drawn to an A2B adenosine receptor agonist compound identified by the method of claim 16 wherein the compound caused more new cells to grow in the first sample in comparison to the second sample.

Grant et al. are relied upon to teach the location of A2B receptors in human retinal endothelial cells. They teach culturing human retinal endothelial cells and administration of known agonists and antagonists of A2B receptors to said cells. They do not necessarily teach motivation for development of new A2B agonists and antagonists to the A2B receptor. They further taught design of an antisense to the A2B receptor, a known antagonist of receptor activity.

Kvanta et al. teach localization of A2B receptors in the rat "ciliary body but not in any other structure within the rat eye" (p. 598, col. B). They further teach "the roles of A2 receptors in the retina are poorly understood, but it has been suggested that A2, receptors are involved in the regulation of retinal blood flow.... Recently, an alternative role for adenosine in the inner retina has been proposed, namely that it could participate in the development of hypoxia-induced retinal neovascularization.... the precise role of adenosine and its receptors, particularly in the

hypoxic retina, merits further study." (P. 601, col. B) Thus they are relied upon to teach motivation for further study of the role of adenosine receptors, including A2B, in the rat retina.

Kim et al., Klotz et al. And Kemp et al. are all relied upon to teach motivation for design of novel agonists and antagonists to the A2B receptor:

Kim et al. teach on page 2835, of all the adenosine receptors, "the adenosine A2B receptor is the poorest characterized subtype of adenosine receptors. Whereas for the other subtypes selective agonists, antagonists, and radiolabeled ligands are available, no such compounds are known for the A2B receptor. For pharmacological studies, both selective agonists and antagonists are needed. An A2B selective antagonist may prove useful in the treatment of asthma." Although they do not specifically teach identification of antagonists or agonists using a retinal cell assay, they do teach (in view of the open "comprising" claim language) a molecular modeling/computational method suitable for development of a potential agonist/antagonist prior to the step of testing said compound in cell culture.

Klotz et al. is relied upon to teach subcloning of A2B receptors into CHO cells for testing. They teach that "currently, no high-affinity agonists or antagonists are available for the A2B adenosine receptor.... the pharmacological profile for antagonists identified XAC as the most potent compound at the human A2B receptor." (P. 8)

Kemp et al. is relied upon to teach on page 1799 "In conclusion, the present study provides strong circumstantial evidence that relaxation of human small resistance-like coronary arteries by adenosine is mediated by a2B receptors which are coupled to K+ channels to mediate

part of the response. A more definitive demonstration that A2B receptors mediate coronary vasodilatation to adenosine in humans, however, awaits the development of selective A2B receptor antagonists."

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to assay a potential A2B agonist or antagonist in cultured human retinal endothelial cells for identification of such a compound as an agonist or antagonist of A2B since Grant et al. taught administration of an antisense to A2B to human retinal endothelial cells in culture and Kim et al., for instance, taught methods for design of other potential A2B agonists or antagonists to A2B.

One of ordinary skill in the art would have been motivated to design new high-affinity A2B agonists or antagonists since Kim et al., Klotz et al, Kemp et al, Kvanta et al, and Grant et al. all specifically taught the need for specific A2B agonists and antagonists for both further characterization of the receptor and its role in different physiological processes, including the function of the retina (Grant et al. and Kvanta et al.).

One of ordinary skill in the art would have had an expectation of success to design potential A2B agonists and antagonists, such as the antisense taught by Grant et al, or via the computer modeling taught by Kim et al., test said compounds on human retinal endothelial cells as taught by Grant et al. and categorize such molecules as an agonist or antagonist based on certain physiological readouts such as taught by Grant et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

SEAN McGARRY
PRIMARY EXAMINER

M. M. Schmidt
November 4, 2001

Attachment for PTO-948 (Rev. 03/01, or earlier)
6/18/01

The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.